Familial Aggregation of Hodgkin Lymphoma and Related Tumors

Lynn R. Goldin, Ph.D.[1]
Ruth M. Pfeiffer, Ph.D.[2]
Gloria Gridley, M.S.[2]
Mitchell H. Gail, M.D., Ph.D.[2]
Xinjun Li, Ph.D.[3]
Lene Mellemkjaer, M.Sc., Ph.D.[4]
Jørgen H. Olsen, M.D., D.M.Sc.[4]
Kari Hemminki, M.D., Ph.D.[3,5]
Martha S. Linet, M.D.[6]

[1] Genetic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland.

[2] Biostatistics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland.

[3] Department of Biosciences at Novum, Karolinska Institute, Stockholm, Sweden.

[4] Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark.

[5] Division of Molecular Genetic Epidemiology, German Cancer Research Center, Heidelberg, Germany.

[6] Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland.

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The Swedish Family-Cancer Database was created by linking registers maintained at Statistics Sweden and the Swedish Cancer Registry.

Address for reprints: Lynn R. Goldin, Ph.D., Genetic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Boulevard, MSC 7236, Bethesda, MD 20892-7236; Fax: (301) 402-4489; E-mail: goldinl@mail.nih.gov

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BACKGROUND. The importance of genetic factors in the etiology of Hodgkin lymphoma (HL) has been suggested by family and population studies. However, the spectrum of malignancies associated with common genetic etiology and the effects of gender and age on familial risk have not been established.

METHODS. Diagnoses of lymphoproliferative malignancies were compared in 15,799 first-degree relatives of 5047 patients with HL versus 32,117 first-degree relatives of 10,078 control probands from Sweden and in 7185 first-degree relatives of 2429 patients with HL versus 27,434 first-degree relatives of 8,495 control probands from Denmark using marginal survival models.

RESULTS. The risk of HL in relatives of patients with HL was increased significantly in both populations, with relative risks of 3.47 (95% confidence interval [95% CI], 1.77–6.80) in Sweden and 2.55 (95% CI, 1.01–6.45) in Denmark and a pooled estimate of 3.11 (95%CI, 1.82–5.29). In Sweden, risks for relatives of patients also were increased significantly for chronic lymphocytic leukemia and non-Hodgkin lymphoma (in males). Relative risks were higher in males compared with females and in siblings of patients compared with parents and offspring of patients. Relatives of patients with earlier-onset disease were at higher risk for HL.

CONCLUSIONS. HL has an important familial component, which is stronger in families of affected individuals age < 40 years, in males, and in siblings, and it is shared with some (but not other) lymphoproliferative malignancies. The cumulative lifetime risks are very small, however, for the development of HL de novo or in first-degree relatives of affected patients. ***Cancer* 2004;100:1902–8.**
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KEYWORDS: Hodgkin lymphoma, lymphoproliferative tumors, familial aggregation, case-control study, linked registries.

Hodgkin disease, recently designated Hodgkin lymphoma (HL) in the World Health Organization Classification system,[1] is an uncommon form of lymphoma. The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) population-based registries estimate that 7600 new cases are diagnosed in the United States annually.[2] Clues about the etiology of HL have been suggested by the bimodal age distribution; by higher risks in males, in persons with higher socioeconomic status, and in smaller families; and by the

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occurrence of Epstein–Barr virus in HL tumor cells.[3] Genetic factors are suggested by reports of multiply affected families from case series,[4–6] a twin study,[7] a case–control study,[8] and population registry studies performed in Utah,[9] Denmark,[10] Israel,[11] and Sweden.[12–14]

Despite evidence suggesting a familial risk component of HL, questions remain regarding the spectrum of tumors associated with HL and the effects of gender and age at diagnosis on familial risk. The availability of a very large familial cancer database in Sweden[15] and a similar large database in Denmark allowed us to quantify the degree of familial aggregation of HL and related lymphoproliferative (LP) malignancies using population-based data. An earlier study of the Swedish database found significant heritability of HL when comparing risks in first-degree relatives with incidence rates in the general population.[12] The current study is unique in several ways compared with earlier epidemiologic studies. First, previous investigations often considered all leukemias and lymphomas together, due to small sample sizes. Second, earlier studies did not compute risks separately for subgroups (such as those based on gender or age) of patients with HL or their relatives. Third, none of the studies evaluated the risks of familial aggregation simultaneously for the entire spectrum of LP malignancies. Taking advantage of the large populations, we assessed risk not only for HL but also for other types of LP tumors separately in relatives of patients with HL. Instead of procedures that rely on external population rates, we used a case–control design that compared the risk in first-degree relatives of patients with HL with the risks in first-degree relatives of matched control individuals. Our approach accounted for correlation among related individuals, truncation in the data due to start dates of cancer registration, and complete ascertainment of all patients with HL in the population. We also incorporated heterogeneity in aggregation by gender, type of relative, and age at onset of the HL case proband. Furthermore, we conducted our analysis in two different populations, one in Sweden and one in Denmark; this feature of the study serves to strengthen our findings.

For HL patients and clinical practitioners, our risks are derived from large numbers and are population based, so they are more accurate compared with estimates derived from small clinical samples or epidemiologic studies of highly selected populations. Our findings regarding the spectrum of LP malignancies that aggregate in families also inform strategies for mapping susceptibility genes in high-risk families and testing candidate genes in families and populations.

MATERIALS AND METHODS

Swedish Family-Cancer Database

The Swedish Family-Cancer Database has been described previously.[15] In brief, Sweden maintains a multigenerational register that includes individuals born from 1932 onward along with parents linked to these individuals. This registry has been linked to the Swedish Cancer Registry (in which malignancies occurring between 1958 and 1998 are registered). Approximately 50% of offspring who died before 1991 (and 12% of offspring with malignant disease) do not have links to parents. All offspring who died before 1960 are missing from the database. The current version of the database from which we drew our samples contains 10.2 million individuals and includes 75% of all tumors registered in the Swedish Cancer Registry. Demographic and vital status information was obtained by linking the Family-Cancer Database to the nationwide census and death notification databases, respectively.

Danish Registries

A similar database of case patients with LP tumors, control individuals, and relatives was created using the Danish Cancer Registry and the Danish Central Population Registry (CPR). The Danish Cancer Registry became a nationwide registry in 1943, but we limited the selection of LP tumor cases to those diagnosed after April 1, 1968, because patients with malignant disease who died before that date could not be linked to the CPR. The CPR contains links of offspring to parents (and vice versa) starting with all children born in 1968 as well as linkages (also starting in 1968) among family members who were living at the same address.

Study Design

For the case group, we selected all individuals from the Swedish Family-Cancer Database who had a first primary diagnosis of HL (International Classification of Diseases Seventh Revision code 201). For each case, two malignancy-free control individuals who matched the case in terms of gender, year of birth, and county of residence were chosen from the Family-Cancer Database. Matching by county of residence controlled for regional variability over time in the reporting of malignancies to the central registry. For each case and control, all first-degree relatives were included in the data set. We analyzed data for 5047 HL probands, 10,078 control probands, and first-degree relatives of these case and control probands. To create a similar database of cases from the Danish registries, all individuals with HL diagnosed between 1968 and 1997 as

either a first or second primary diagnosis were selected from the Danish Cancer Registry. Four malignancy-free control individuals per case were chosen from the CPR. All first-degree relatives of case patients and control individuals were identified by linking the individual's identification number to the relatives in the CPR. Case patients and control individuals with no relatives identified from the linkage were removed from the study, and duplicate controls also were removed. This resulted in fewer than four control individuals per case patient in the final sample. All diagnoses were ascertained for the relatives by linking them to the Cancer registry. We analyzed data for 2429 HL probands, 8495 control probands, and first-degree relatives of these case and control probands. We classified relatives as *affected* if they had a first, second, or third primary cancer registration involving the tumor of interest.

Statistical Analysis

The statistical approach was based on a model proposed by Liang[16] and has been described in detail elsewhere.[17] In brief, we applied a marginal survival model in which t_{ij} denotes the age at onset of disease or the age at censoring for member j in family i. The outcome t_{ij} is modeled by a marginal proportional hazards model, $\lambda(t_{ij}|X_{ij}, Z_{ij}) = \lambda_0(t_{ij})\exp(\beta X_{ij} + \gamma Z_{ij})$. The term λ_0 represents the arbitrary baseline hazard function, X_{ij} denotes measured covariates for a given individual (in the current analysis, gender, type of relative, and age at onset for the proband), and Z_{ij} is an indicator of the proband's disease status ($Z_{ij} = 1$ if the proband of family i is a case and 0 otherwise). Testing for familial aggregation corresponds to testing the null hypothesis H_0: $\gamma = 0$ (i.e., hazard ratio = 1). The parameters β and γ were estimated under a working independence assumption (PROC PHREG; SAS Version 8.02; SAS Inc., Cary, NC). The robust sandwich covariance matrix accounts for the dependence of the family members.[18] We use the term *relative risk* to denote the hazard ratio defined above.

An individual entered the risk period at his or her age at the start of cancer registration (1958 in Sweden) or population registration (1968 in Denmark) or at the date of birth (or immigration) if birth (or immigration) occurred after the start date for registrations. Censoring events were death, emigration, or the end of the data acquisition period (1998 for Sweden and 1997 for Denmark). Individuals were not censored if they developed a malignancy other than the LP tumor being tested, because they still would be at risk for developing LP as a subsequent tumor. We tested separately for increased risk for HL, non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia (CLL), and multiple myeloma (MM) in relatives and also tested for increased risk of developing *any* one of the four tumors considered together. We also considered other factors affecting risk by including gender, type of relative, and age of disease onset in the case proband in the same model. We compared the risk in siblings with the risk in parents and offspring, because a recessive gene would predict a higher risk in siblings compared with parents and offspring, whereas a dominant gene would predict equal risks in siblings, parents, and offspring. We used an age at diagnosis of 40 years as a cutoff point for early onset versus late onset in probands. This cutoff age reflects the bimodal age distribution observed among patients with HL in the Nordic countries[19] and in the United States,[2] where age-specific incidence rates increase in early adulthood and then decline rapidly to a nadir at about age 40 years before rising again with increasing age. Data were analyzed for each population both separately and in a pooled manner. To test for anticipation, we compared the average age at diagnosis of HL in parents and offspring of case patients. In addition, we computed Kaplan–Meier estimates of risk of CLL by age and tested for homogeneity of parent and offspring strata using nonparametric tests (PROC LIFETEST; SAS Version 8.02).

In an exploratory analysis, we examined whether other disease types (including leukemias other than CLL) were more common in relatives of patients with HL than in control relatives using standard chi-square 2×2 table comparisons.

RESULTS

General Description

In Sweden, 59% of the 5047 case patients were males. The age at diagnosis followed a typical bimodal distribution, with a peak among individuals in their early 20s and a second peak among individuals in their early 60s. Probands were born between 1879 and 1994 (mean year of birth, 1934). In Denmark, 62% of the 2429 probands were males, and 99% of the case patients had HL as a first primary malignancy. Probands were born between 1897 and 1994 (mean year of birth, 1951). The age distribution at diagnosis was unimodal, with a peak among individuals in their early 20s. The younger age distribution and lack of an age peak among individuals in their early 60s in Denmark was attributable to the restriction of case patients with LP to individuals who were diagnosed with HL between 1968 and 1997 and who also could be linked to relatives. In both data sets, approximately 50% of first-degree relatives were offspring. In Sweden, 25% each were parents and siblings, and in Denmark, 30% were parents, whereas 20% were siblings.

TABLE 1
Counts and Percentages of Lymphoproliferative Malignancies in Case and Control Relatives

	No. of relatives (%)			
	Sweden		Denmark	
Malignancy	Case group (n = 15,799)	Control group (n = 32,117)	Case group (n = 7185)	Control group (n = 27,434)
HL	32 (0.20)	18 (0.06)	12 (0.17)	17 (0.06)
NHL	46 (0.29)	70 (0.22)	9 (0.13)	33 (0.12)
CLL	16 (0.10)	14 (0.04)	5 (0.07)	11 (0.04)
MM	13 (0.08)	27 (0.08)	4 (0.06)	13 (0.05)
Any LP	107 (0.68)	128 (0.40)	30 (0.42)	74 (0.27)

HL: Hodgkin lymphoma; NHL: non-Hodgkin lymphoma; CLL: chronic lymphocytic leukemia; MM: multiple myeloma; LP: lymphoproliferative.

TABLE 2
Relative Risks and 95% Confidence Intervals for Development of Lymphoproliferative Tumors Based on Survival Analyses of Case Relatives versus Control Relatives, with Stratification by Gender[a]

Group analyzed	Total no.	Relative risk (95% CI)				
		HL	NHL	CLL	MM	Any LP
Sweden						
All	47,916	3.47 (1.77–6.80)	1.32 (0.91–1.91)	2.30 (1.13–4.70)	0.98 (0.50–1.90)	1.67 (1.27–2.21)
Males	23,989	3.56 (1.61–7.89)	1.70 (1.05–2.77)	3.13 (1.21–8.06)	1.44 (0.58–3.59)	2.18 (1.54–3.11)
Females	23,927	3.29 (1.07–10.10)	0.91 (0.49–1.67)	1.48 (0.47–4.64)	0.65 (0.24–1.80)	1.13 (0.74–1.76)
Denmark						
All	34,619	2.55 (1.01–6.45)	1.04 (0.50–2.17)	1.75 (0.60–5.10)	1.07 (0.37–3.06)	1.57 (0.97–2.52)
Males	17,805	2.85 (0.94–8.62)	1.06 (0.43–2.63)	—	—	1.74 (0.98–3.11)
Females	16,814	2.09 (0.51–8.54)	1.00 (0.28–3.52)	—	—	1.30 (0.61–2.77)
Combined						
All	82,535	3.11 (1.82–5.29)	1.26 (0.90–1.75)	2.11 (1.18–3.77)	1.02 (0.57–1.80)	1.65 (1.30–2.10)
Males	41,794	3.31 (1.75–6.26)	1.53 (1.01–2.32)	2.28 (1.09–4.76)	1.67 (0.79–3.21)	2.06 (1.53–2.78)
Females	40,741	2.75 (1.18–6.41)	0.92 (0.53–1.60)	1.90 (0.74–4.90)	0.52 (0.20–1.37)	1.18 (0.81–1.72)

95% CI: 95% confidence interval; HL: Hodgkin lymphoma; NHL: non-Hodgkin lymphoma; CLL: chronic lymphocytic leukemia; MM: multiple myeloma; LP: lymphoproliferative.
[a] Estimates for whole samples were controlled for gender. Combined estimates (Sweden/Denmark) also were controlled for study.

Risk of LP Tumors in First-Degree Relatives

Table 1 shows the counts and percentages of first-degree relatives with each of the four types of LP tumors. All major types of LP tumors except for MM were more common in case relatives than in control relatives. The results for HL were similar in Sweden and Denmark, whereas the crude prevalence rates for NHL, CLL, and MM were lower among relatives from the Danish sample compared with relatives from the Swedish sample. This finding probably is attributable to differences in age and follow-up duration in the two samples; both case patients and relatives tended to be younger in Denmark.

Table 2 shows relative risk data, comparing relatives of case patients with relatives of control individuals in each of the samples, in the combined Swedish/Danish sample, and with stratification according to gender. The risk of developing HL was increased significantly among case relatives in both samples and in both males and females. The combined relative risk was 3.11. In Denmark, CLL was increased nonsignificantly for relatives of case patients. In Sweden, NHL was increased significantly among male relatives, and CLL was increased significantly among all relatives. When all LP tumors were considered together, the resulting combined relative risk of 1.65 was highly significant, with similar estimates in both populations. Gender-related differences also were significant. However, the gender of the proband was not a significant predictor of risk in either population.

In each sample, we assessed whether the type of relative (siblings compared with parents and offspring) or the age at diagnosis of the proband (age

TABLE 3
Relative Risks and 95% Confidence Intervals for Development of Lymphoproliferative Tumors Based on Survival Analyses of Case Relatives versus Control Relatives, with Stratification by Type of Relative

	Relative risk (95% CI)			
	Sweden		Denmark	
Malignancy	Siblings (n = 11,691)	Parents/offspring (n = 36,225)	Siblings (n = 7102)	Parents/offspring (n = 27,517)
HL	4.26 (1.49–12.17)	3.10 (1.28–7.48)	6.21 (1.68–22.92)	1.17 (0.26–5.21)
NHL	2.18 (0.77–6.18)	1.28 (0.82–1.83)	—[a]	1.01 (0.46–2.20)
CLL	—[a]	2.17 (1.02, 4.61)	—[a]	1.29 (0.41–4.07)
MM	—[a]	1.01 (0.52, 1.97)	—[a]	1.16 (0.39–3.43)
Any LP	3.11 (1.53–6.31)	1.49 (1.10–2.01)	4.87 (1.66–14.23)	1.14 (0.67–1.94)

95% CI: 95% confidence interval; HL: Hodgkin lymphoma; NHL: non-Hodgkin lymphoma; CLL: chronic lymphocytic leukemia; MM: multiple myeloma; LP: lymphoproliferative.
[a] Insufficient data.

TABLE 4
Relative Risks and 95% Confidence Intervals for Development of Lymphoproliferative Tumors Based on Survival Analyses of Case Relatives versus Control Relatives, with Stratification by Age of Proband at Diagnosis

	Relative risk (95% CI)			
	Sweden: age of proband at diagnosis (yrs)		Denmark: age of proband at diagnosis (yrs)	
Malignancy	≤ 40 (n = 26,951)	> 40 (n = 20,965)	≤ 40 (n = 28,001)	> 40 (n = 6618)
HL	4.25 (1.85–9.77)	2.56 (0.90–7.25)	3.51 (1.30–9.41)	0.59 (0.06–5.20)
NHL	1.35 (0.84–2.17)	1.26 (0.69–2.30)	0.71 (0.30–1.69)	—[a]
CLL	2.38 (1.0–5.74)	2.14 (0.62–7.39)	—[a]	—[a]
MM	1.32 (0.59–2.93)	0.53 (0.15–1.93)	—[a]	—[a]
Any LP	1.86 (1.32–2.61)	1.41 (0.90–2.21)	1.41 (0.84–2.35)	3.15 (0.87–11.39)

95% CI: 95% confidence interval; HL: Hodgkin lymphoma; NHL: non-Hodgkin lymphoma; CLL: chronic lymphocytic leukemia; MM: multiple myeloma; LP: lymphoproliferative.
[a] Insufficient data.

≤ 40 years vs. age > 40 years) predicted case–control differences among relatives. A significantly increased risk among siblings (compared with parents and offspring) was found for HL and for all LP tumors considered together in both populations and in the combined sample. Table 3 shows the stratified risks among siblings compared with parents and offspring. For HL, the difference was especially striking in Denmark (relative risk, 6.21 for siblings compared with 1.17 for parents and offspring). The age at diagnosis of the proband was not a statistically significant predictor of case–control differences, but Table 4 shows that the risks of HL were higher among relatives of case patients with early-onset disease in both populations. In addition, relatives of younger individuals with HL also experienced earlier onset (data not shown). The HL case sample was younger in Denmark, where 70% of the probands belonged to the early-onset group. The relative risk of HL (3.51) was higher in the early-onset group than in the sample as a whole (2.55), and 13 of the 14 cases of HL that were observed in relatives occurred in the early-onset subgroup. The numbers of other types of LP tumors were too limited to warrant firm conclusions, although there was no obvious aggregation in the younger case families. In contrast to the sample from Sweden, the Danish sample indicated that relatives of case patients with later onset of disease had an increased risk of being diagnosed with any one of the four LP tumors considered as a group. However, the sample was small, and the resulting confidence interval was large. Age at onset among familial case patients in these samples was younger than age at onset among sporadic case patients. In both samples, case patients with familial HL had an earlier age at onset than did case patients with HL from control families, although the difference was not significant.

An earlier study of the Swedish database found

that HL offspring have an earlier age at diagnosis than do their affected parents,[12] a phenomenon known as *anticipation*. Results based on parent-offspring case pairs in these samples were consistent with the occurrence of anticipation (the average age at diagnosis was 43.9 for parents and 26.9 for offspring in the combined sample), but we cannot rule out an ascertainment bias. Parents with an early age at onset of HL would not appear in the sample if they were diagnosed before cancer registration was initiated. Similarly, at the end of case selection in 1997 or 1998, many offspring were not old enough to develop HL. Anticipation would be unbiased if a difference were found in the survival curves between parental and offspring generations. When the samples from Sweden and Denmark are combined, life table analysis reveals no difference between parents and offspring (data not shown).

Other types of leukemia (ALL, AML, and CML) were rare and did not aggregate in HL case families. An exploratory investigation of other solid tumor sites revealed that in Sweden, tumors of the breast ($P = 0.006$), ovary ($P = 0.004$), and kidney ($P = 0.05$) were more common in case relatives compared with control relatives. In Denmark, tumors of the uterine cervix ($P = 0.02$) and the brain ($P = 0.02$) were more common in HL case relatives compared with control relatives.

DISCUSSION

We have shown significant familial aggregation of HL and other related conditions. The large sample sizes in the current study allowed us to incorporate heterogeneity in aggregation for several factors, such as gender, type of relative, and age at onset of the proband. We found that the familial risks were higher in males than in females, a finding that is consistent with earlier publications showing that familial case patients were more likely to be male.[6,8] Patients with familial HL had an earlier than average age at diagnosis; risk also was increased among relatives of patients who had early-onset HL compared relatives of patients who had later onset of HL, although these differences were not statistically significant. Hemminki et al.[14] applied a standardized incidence ratio method to cases of onset of HL occurring in 1991 and later to cases from the Swedish database and found an increased risk of HL in offspring and siblings of case patients and slightly higher risks in offspring and siblings of case patients with onset at age < 50 years. Siblings had a significantly higher risk of developing HL or of developing any LP tumor compared with parents.[4] This finding, which is consistent with clinical studies, suggests the importance of recessive genes or certain common environmental factors.

The current study also provides independent evidence of shared genetic etiology among LP tumors. Although some earlier investigations found increases in all lymphomas or leukemias combined,[8,11] the current study is unique in that sample sizes were sufficient for testing hypotheses regarding other LP tumor types as separate entities. Some aggregation of HL and NHL in particular may be due to misclassification,[20] but common etiology between HL and other LP tumors also is implied from other data. For example, there are reports of patients who develop composite HL/NHL or HL/CLL in which the two tumors coexist within the same biopsy sample and are shown to be clonally related.[21] In addition, patients with HL have a high risk of developing NHL as a second tumor,[22] and patients with NHL have an increased risk of developing HL as a second tumor.[23] Patients with CLL also are at an increased risk of developing HL and NHL (Richter syndrome); it is believed that the second malignancies derive from clonal evolution.[24] It is noteworthy that patients with MM do not consistently develop second LP malignancies, and we also found no increased familial risk of MM in the relatives of HL patients.

To eliminate possible ascertainment bias, some studies start the follow-up period of the relatives at the date of birth or diagnosis of the case.[25] In the current study, case and control probands were matched, so any bias should have been similar in case and control relatives. Although many individuals born before 1991 are missing from the Swedish database,[15] relative risks based only on outcomes from 1991 and later, for which we know that the database is essentially complete, were very close to those computed when all of the data were included. This suggests that the familial aggregation observed was not a result of survival bias.

It would be interesting to determine whether certain subtypes of HL or NHL are more likely to aggregate in HL families. However, both registries began including histology codes only in more recent years and do not include information on immunophenotype, morphology, cytogenetics, cytochemistry, or other important aspects incorporated into the recent World Health Organization classification of hematopoietic neoplasms and related disorders.[1]

It is important to note that although the risk for relatives of patients with HL is increased significantly compared with the risk for relatives of control individuals, the absolute excess risk of developing HL is small. Based on SEER data,[2] the lifetime risk for developing HL is estimated to be 0.24% (0.26% for males and 0.22% for females). Even if we use the combined Swedish/Danish relative risk of 2.89 (3.15 for males and 2.48 for females), the absolute lifetime risk for all

first-degree relatives is increased only to 0.69% (0.81% for males and 0.55% for females).

Aside from associations with HLA types, specific genes that cause susceptibility to HL have not been identified to date.[26] The significant familial aggregation shown here and in other studies justifies the application of gene mapping approaches in high-risk families and provides strong clues regarding which families are likely to have a genetic etiology. It is likely that the strongest genetic effects will be found in families with young-onset sibling probands. The evidence for shared genetic etiology among LP tumors also suggests that within families, the same gene may lead to the expression of a range of phenotypes.

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